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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	4

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,147	LA THANGUE ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Seq. alignment* .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that claim 12, 16, and 20 should be included with the elected invention because claims 12m 16, and 20 are also drawn to the polypeptide of group I. This is not found persuasive because the claims as written are interpreted as drawn to method of using the polypeptides in treatment.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-20 are pending and claims 1-11 are examined on merits.

Sequence Rules

This application contains sequence disclosures for example at Fig. 1 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. 37 CFR 1.821(a) presents a definition for "nucleotide and/or amino acid sequences." The instant application contains an unbranched specifically defined sequence of more than ten nucleotides. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Branched sequences are specifically excluded from this definition. Sequences with fewer than four specifically

defined nucleotides or amino acids are specifically excluded from this section. "Specifically defined" means those amino acids other than "Xaa" and those nucleotide bases other than "n" defined in accordance with the World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25: Standard for the Presentation of Nucleotide and Amino Acid Sequence Listings inPatent Applications (1998), including Tables 1 through 6 in Appendix 2 (see MPEP § 2422).

Specification

The disclosure is objected to because the specification does not describe the peptides being used in the X-axis of the instant Fig. 3. The disclosure at pages 29-30 appears to say that the peptides listed as H-H7 at Fig. 1 are same as the peptides used at Fig. 3 but the label in Fig. 1 and Fig. 3 have different symbols, which causes confusion.

Appropriate correction is required.

Claim Objections

Claims 2-9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 2 describes the inherent characteristic of the peptide in claim 1, and fails to further limit the subject matter. This rejection affects any claims depends from claim 2. Further, claim 3 does not further limit the claims it depends from, i.e. claim 1 and claim

2. Claim 1 is drawn to SEQ ID NO:1 but claim 3 is drawn to two smaller fragments within SEQ ID NO:2. Claim 4 has the same problems as claim 3.

Claim 5 depends on claim 1 drawn to a polypeptide consisting essentially of SEQ ID NO:1 but a polypeptide in claim 5 is not limited to a polypeptide consisting essentially of SEQ ID NO:1 and since claim 6 depends on objected claim, claim 6 is also objected.

Claim 7 depends on claim 1 which is limited to polypeptides consisting essentially of SEQ ID NO:1. However, claim 7 broadens claim 1 by reciting the limitation "comprises" the protein defined in claim 1. The dependent claims 8 and 9 are also objected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites "derived" but it is not clear what the metes and bounds are.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a pharmaceutical comprising the peptide claimed in the instant claim 1. Inherent in pharmaceutical is in vivo use. The specification at page 19 asserts that the peptides claimed could be used in treatment of cancer or psoriasis. The art recognizes that treating cancer and/or psoriasis is not a trivial matter. Fig. 1 shows that several peptides H (SEQ ID NO:1), H2, H3, H5, and H5) dimerize and Fig. 3 shows that some peptides induce cell death in vitro cells.

One cannot extrapolate the teachings of the specification to the claimed invention because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para of column 1). Fan et al (2003, Proc. Natl. Acad. Sci. USA. vol. 100, pages 3386-91) teach that psoriasis is an autoimmune disease and what mediates such an undesirable immunological response is not well understood as of year 2003. Note the 2nd paragraph of page 2286, left column. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put

expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In addition, anti-tumor agents and those that prevent, reduce, retard or eliminate secretion of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promotor producing cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established.

The *in vitro* data at Fig. 3 cannot be correlated to the invention as claimed, because the *in vitro* cells are continuously in contact with peptides in the assays, and are not subjected to the defense of the body. In addition, characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences

between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Thus, based on the cell culture data presented in the specification, it could not be predicted that the claimed invention could treat cancer or psoriasis *in vivo*. The specification provides insufficient guidance with regard to theses issues and provides no

working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed peptide or its fragments as a pharmaceutical with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat 5,863,757 (filing date of May 11, 1995).

The claims are interpreted as drawn to a polypeptide consisting essentially of SEQ ID NO:1. Based on the specification at page 6, lines 19-27, any polypeptide smaller than the full length, i.e., 410 amino acid (the instant SEQ ID NO:1 corresponds to amino acids #163-199 of a 410 amino acids protein, see the sequence aligment) appears to be within the scope of instant claims. 5,863,757 teach SEQ ID NO:11 at columns 35 and 36, an 72 amino acid polypeptide consisting essentially of instant SEQ

ID NO:1. Note the sequence alignment. The function described in the instant claim 2 is the inherent property of the polypeptide taught by 5,863,757.

Claims 2-9 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat 5,859,199 (filing date of May 15, 1996).

The claims as written depend on the base claim 1. Since the claims do not further limit the base claims, the Office treats the claims as independent for compact prosecution. Further the Office interprets the scope of the claims as drawn to any peptides smaller (even one amino acid less) than the full-length DP-1. See above 102 (e) rejection for further clarification. In summary, the claims are interpreted as drawn to a polypeptide comprising minimum amino acid sequence (H5 in the instant Fig. 1) necessary for competitive inhibition of heterodimerization of the full length DP protein to an E2F protein. US Pat 5,859,199 teaches 5 different polypeptides known as DP-3, splice variants of DP-1, which are smaller than the 410 amino acids DP-1 but has the necessary sequence (H5) for binding to E2F, thus anticipating the instant claims. See the sequence alignment.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
June 10, 2003

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600